REMARKS

Applicants petition herein for revival of the instant application for unintentional abandonment. Applicants did not receive the Office Action mailed November 30 2007 by the USPTO.

On July 8, 2008, the Examiner telephoned Applicants' representative, Pamela C. Ball, to inquire as to Applicants' intent to reply to the Office Action mailed November 30, 2007. Applicants' representative informed the Examiner that the Office Action was not received by Applicants. The Examiner informed Applicants' representative that because the case was available on Public PAIR, Applicants were responsible for a timely reply. The Examiner indicated that a Notice of Abandonment would be mailed. Applicants note that the Examiner telephoned after the 6 month deadline expired.

The Notice of Abandonment prepared by the Examiner was mailed July 11, 2008. In the Notice of Abandonment, the Examiner records the substance of the interview as follows: "Applicant indicated that no reply has been sent to the most recent office action." Applicants respectfully point out that Applicants' representative clearly noted to the Examiner that *no such office Action had been received* and lack of receipt of the office Action was the sole reason that no reply had been submitted. Applicants have since retrieved the November 30, 2007 Office Action from Public PAIR and submit the following response.

In the instant Action, claims 17-19, 22, 26, 31 and 32 are listed as pending and all claims are rejected. No claims are amended or cancelled in this reply. Applicant expressly reserves the right to reclaim the canceled subject matter in a subsequent application.

CLAIM REJECTIONS

1. Claim Rejections – 35 U.S.C. § 103(a)

1A. Rejection of claims 17-19 under 35 U.S.C. 103(a)

On pages 2-6 of the instant Action, the Examiner has maintained the rejection of claims 17-19 under 35 U.S.C. § 103(a) as being unpatentable over Gordon *et al.* (PCT International Publication WO 00/39130, referred to hereinafter as "Gordon") in light of Rybak (PCT International Publication WO 01/64197, referred to hereinafter as "Rybak"). In brief, the Examiner alleges that as Gordon discloses the farnesyl transferase inhibitor (FTI) of instant claims 17-19, and as Rybak discloses therapeutic combinations of anthracyclines and FTIs, it would have been obvious to the skilled artisan to provide a pharmaceutical composition comprising an FTI according to Gordon and an anthracycline such as doxorubicin to treat NPC.

The complete details of the Examiner's comments are found on pages on pages 2-4 of the instant Action and the Examiner's comments upon Applicants' previous reply are found on pages 4-6 of the instant Action; these comments are not reiterated in full in this reply.

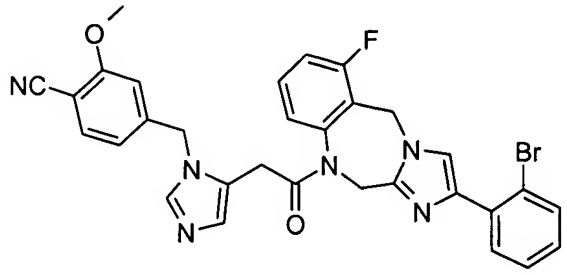
1B. Claims 17-19 are not obvious over Gordon in light of Rybak

Applicants again respectfully submit that the invention of claims 17-19 is not obvious over Gordon in light of Rybak. Applicants incorporate all arguments presented in reply to this rejection from the previous reply (mailed September 26, 2007) and offer the following additional comments.

Firstly, Applicants note that claims 17-19 are directed to a composition; these claims are not directed to a method of use for the composition. Applicants will address rejections regarding the use of the composition of claims 17-19 to treat nasopharyngeal cancer in section 2 of this paper.

Applicants again note that neither Gordon nor Rybak teach or suggest the **particular** FTI/anthracycline combination recited in instant claim 17. Gordon teaches thousands of FTI compounds; Applicants submit that the Examiner has failed to point

out the teachings of Gordon that would guide the skilled artisan to select ***any*** single FTI compound from among the multitude of compounds presented, let alone the particular claimed compound. This defect is not cured by Rybak as Rybak discloses even more FTI compounds and fails to provide any data or teachings to direct the skilled artisan to select particular compounds. There is simply no teaching or suggestion in Gordon and/or Rybak that would lead the skilled artisan to select any one compound over any other compound presented, let alone the **particular** FTI/anthracycline combination of instant claim 17. It is Applicants' teaching that identifies



and an anthracycline as a desired combination, a selection that was unknown and unappreciated by Gordon and/or Rybak. As recently decided in Boston Scientific v Johnson & Johnson (No. C 02-00790, 2007 WL 2408870 at *13-14 (N.D. Cal. Aug. 21, 2007)), a passing reference to a possible solution does not necessarily imply that it is a viable solution.

Applicants further submit that a reasonable expectation must lead to a predictable result and must be more than the presentation of a laundry list of options with no guidance provided as to which option to choose. Applicants submit that a reasonable expectation of success is not automatically established where the prior art discloses many alternative routes. Art that provides many opportunities for erroneous or unsupported combinations and fails to teach success cannot make obvious the clear choice to make. See Takeda Chemical v Alphapharm (492 F.3d 1350, 1356 (Fed. Cir. 2007)):

"Rather than identify predictable solutions [for antidiabetic treatment], the prior art disclosed a broad selection of compounds ***any one of which*** could have been selected as a lead compound for further investigation." (emphasis added)

In a similar vein, neither Gordon nor Rybak, nor the combination of the two, which provide thousands of possible FTI compounds and anthracycline compounds, provide any direction to select the ***particular*** FTI/anthracycline combination as described in instant claim 17. Absent the teaching of the instant invention, the skilled artisan could only guess at which FTI compound to combine with which anthracycline compound. With so many options presented in Gordon and/or Rybak, the options to choose a FTI/anthracycline combination *other* than that of instant claim 17 far outweigh the option to choose the combination of instant claim 17. Applicants submit that the Examiner has again failed to establish a prima facie case for obviousness as required under 103(a).

On pages 4-6 of the instant Action, the Examiner presents reasons as to why Applicants' arguments of September 26 2007 were found non-persuasive. The Examiner points out that according to 35 U.S.C., the prior art need not explicitly teach every limitation of the claimed invention in one reference, noting that "the art must merely suggest the usefulness of the claimed combination. In the instant case, it is already known that it is advantageous to combine a farnesyl transferase inhibitor and an anthracycline."

Applicants respectfully disagree. Applicants submit that neither Gordon nor Rybak nor the combination of the two, actually demonstrate any "advantage" to the combination of FTI/anthracycline; Gordon merely teaches thousands of possible FTIs and Rybak provides no data to show that the combination actually offers an advantage over either component alone. In fact, inspection of Rybak shows that a significant reason for the combination of FTI and an anthracycline proposed is to "provide a means for the use of lower dosages of anti-tumor anthracycline derivatives to reduce the potential of adverse toxic side effects to the patient" because "anthracycline derivatives generally display a serious cardiomyopathy at higher doses, which limits the doses at which these compounds can be administered."

Applicants again respectfully submit that Rybak and Gordon fail to provide data demonstrating that the combination of an FTI and an anthracycline actually confer any

anti-tumor effect, let alone an anti-tumor effect upon NPC. Applicants again direct the Examiner to instant Figure 2, which elegantly shows that doxorubicin in combination with FTI Compound A results in a greater decrease in cell viability as compared to doxorubicin or Compound A alone. Applicants submit that the Examiner has assumed that the goal of Rybak is the advantage of Rybak when Rybak has failed to demonstrate that any actual synergy or advantage exists in the combination of FTIs and anthracyclines. It is Applicants' data that provides the missing link, demonstrating that the hoped for synergy in fact can occur.

Applicants submit for consideration the recent issues with Vytorin (see Exhibit A). Vytorin is a combination of simvastatin and ezetimibe. Simvastin works to lower LDL cholesterol by inhibiting synthesis of LDL cholesterol and consequently inhibiting artherosclerosis. Ezetimibe lowers the absorption of ingested cholesterol in the gut and also lowers LDL cholesterol in the blood by increasing absorption of LDL by cells. Each drug therefore reduces the amount of circulating LDL. Since Simvastin also resulted in a decrease in artherosclerosis, it was assumed and expected that the combination of simvastin and ezetimibe would act in concert to reduce artherosclerosis to a greater degree. Studies showed however, that this expectation was incorrect; patients receiving Vytorin did not exhibit a greater decrease in atherosclerosis. Applicants submit that the finding with Vytorin further demonstrate that a goal, such as that of Rybak, does not always and necessarily predict and result in an advantage.

1C. Request for withdrawal of rejection of claims 17-19 under 35 U.S.C. § 103(a)

Applicants submit that, for reasons cited above, claims 17-19 are in no way made obvious by Gordon in light of Rybak. Applicants request the reconsideration and withdrawal the rejection of claims 17-19 under 35 U.S.C. § 103(a).

2. Claim Rejections – 35 U.S.C. § 103(a)

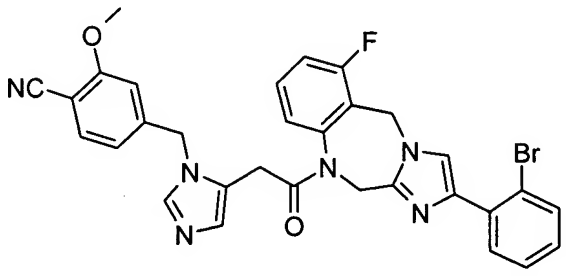
2A. Rejection of claims 22, 26, 31 and 32 under 35 U.S.C. 103(a)

On pages 7-8 of the instant Action, the Examiner has raised new grounds for the rejection of claims 22, 26, 31 and 32 under 35 U.S.C. § 103(a) as being unpatentable over Gordon in light of Rybak in further view of Porter *et al.* (Acta Otolaryngol, 1994, 114:105; referred to hereinafter as "Porter"). In brief, the Examiner alleges that as Gordon and Rybak disclose the FTI/anthracycline combination of the instant invention and Porter discloses a study in which 73% of NPC investigated exhibited increased expression of *ras*, it would have been obvious to the skilled artisan to use a combination of an FTI and an anthracycline to treat NPC. The complete details of the Examiner's comments are found on pages on pages 7-8 of the instant Action and are not reiterated in full in this reply.

2B. Claims 22, 26, 31 and 32 are not obvious over Gordon in light of Rybak and Porter

Applicants respectfully submit that the invention of claims 22, 26 and 31-32 is not obvious over Gordon in light of Rybak and Porter.

Applicants respectfully submit that for the reasons cited above, the Examiner has failed to present a *prima facie* case for obviousness against instant claims 17-19, *i.e.*, the **particular** FTI/anthracycline combination where the FTI is



This failure to identify the particular FTI/anthracycline combination of claims 17-19 is not cured by Porter as Porter simply demonstrates that some NPC carcinomas exhibit high levels of *cmyc* or *ras*. Because the method of use of claims 22, 26, 31 and 32 utilizes the particular FTI/anthracycline combination of claim 17-19, Gordon, Rybak and Porter fail to teach all aspects of the claims. As recited in the MPEP at 2143.03, "to establish

prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F2.d 981, 180 USPQ 580 (CCPA 1974)".

Applicants further submit that this combination of references fails to support a *prima facie* case of obviousness because the references do not teach or suggest to the skilled artisan that the presence of *ras* protein is the key teaching to *knowing* that FTIs and anthracyclines will obviously work in synergy as anticancer agents against NPC. Gordon discusses that intervention of the function of *ras* mediated signal transduction by prenyl transferase inhibitors may be useful in the treatment of cancer. Rybak also postulates that farnesyl transferase inhibitors may be useful as anticancer agents to treat tumors in which *ras* contributes to transformation.

However, Gordon is silent as to the use of anthracyclines as anti-tumor agents at all and Rybak fails to teach or suggest that anthracyclines effect anti-tumor activity via a *ras* mediated pathway. Porter does not cure this defect of Gordon and Rybak as Porter fails to teach or suggest that anthracyclines or FTIs exert a cellular effect upon *ras* mediated pathways or that such an effect is key to the anti-tumor activity attributed to these compounds. Thus the combination of Gordon, Rybak and Porter do not and cannot teach or suggest to the skilled artisan that an anthracycline/FTI combination will necessarily result in an increased anti-tumor effect via a *ras* mediated pathway.

2C. Request for withdrawal of rejection of claims 22, 26 and 31-32 under 35 U.S.C. § 103(a)

Applicants submit that, for reasons cited above, claims 22, 26 and 31-32 are in no way made obvious by Gordon in light of Rybak and Porter. Applicants request the reconsideration and withdrawal the rejection of claims 22, 26 and 31-32 under 35 U.S.C. § 103(a).

Reconsideration of the instant Office Action, entry of the amendments submitted herewith, and allowance of all pending claims are respectfully requested. Prompt and favorable action is solicited.

Respectfully submitted,

Date: 8/27/08

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ACC Statement on ENHANCE Trial

By maureen
Created Jan 16 2008 - 12:23pm

ACC Statement on ENHANCE Trial

January 15, 2008

The ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) trial results were released by Merck and Schering-Plough Pharmaceuticals on January 14, 2008. The results of the trial show no benefit from the combination of ezetimibe (Zetia) and simvastatin (sold together as Vytorin) over simvastatin alone in terms of affecting the rate of atherosclerosis progression.

The study involved 720 patients with heterozygous familial hypercholesterolemia and showed no significant difference in the primary endpoint between patients treated with ezetimibe and simvastatin versus patients treated with simvastatin alone over a two-year period. The study was designed to prove that Vytorin could slow the growth of plaque in carotid arteries supplying the brain more than simvastatin alone. Media reports indicate that the results of the trial show no benefit from the combination of ezetimibe (Zetia) and simvastatin (sold together as Vytorin) over simvastatin alone.

The American College of Cardiology recommends that major clinical decisions not be made on the basis of the ENHANCE study alone.

According to the American College of Cardiology (ACC), this study deserves serious thought and follow-up. The overall incidence rates of cardiac events were nearly identical between both treatment groups, and both medicines were generally well tolerated. There should no be reason for patients to panic. The difference in IMT changes between the simvastatin group and the Vytorin group was 0.006 mm vs. 0.011 mm.

Health care professionals should speak to their concerned patients using this drug. The ACC is also releasing a public statement explaining that this is not an urgent situation and patients should never stop taking any prescribed medications without first discussing the issue with their health care professional. Further research will be needed in this area to provide conclusive evidence about which lipid lowering strategy is preferred (statin alone vs. statin plus ezetimibe).

Furthermore, the ACC notes that this trial is an imaging study and not a clinical-outcome study. Conclusions should not be made until the three large clinical-outcome trials are presented within the next two to three years. The ACC recommends that Zetia remain a reasonable option for patients who are currently on a high dose statin but have not reached their goal. The ACC also

notes that Zetia is a reasonable option for patients who cannot tolerate statins or can only tolerate a low dose statin.

Reports also indicate that the ENHANCE trial has been submitted as an abstract to be presented at the upcoming American College of Cardiology Scientific Session in March, 2008. The late-breaking clinical trial selections by the meeting co-chairs are scheduled to occur in late January.

For more information on the ENHANCE trial, please visit Cardiosource at http://www.cardiosource.com/clinicaltrials/trial.asp?trialID=1640 [1].

Source URL:
http://www.fiercebiotech.com/press-releases/acc-statement-enhance-trial

Links:
[1] http://www.cardiosource.com/clinicaltrials/trial.asp?trialID=1640

Simvastatin

From Wikipedia, the free encyclopedia

Simvastatin (INN) (pronounced /ˈsɪmvəstætɨn/), (marketed under the trade names **Zocor**, Simvastatin, Simlup, Simcard and others) is a hypolipidemic drug belonging to the class of pharmaceuticals called "statins". It is used to control hypercholesterolemia (elevated cholesterol levels) and to prevent cardiovascular disease. Simvastatin is a synthetic derivate of a fermentation product of *Aspergillus terreus*.

Contents

- 1 History
- 2 Uses
- 3 Rationing
- 4 Pharmacology
  - 4.1 Interactions
- 5 Side effects
- 6 Marketing
- 7 Sales
- 8 References
- 9 See also
- 10 External links

History

The development of simvastatin was closely linked with the research and development of Mevacor. Biochemist Jesse Huff and his colleagues at Merck began researching the biosynthesis of cholesterol in the early 1950s. In 1956, mevalonic acid was isolated from a yeast

Simvastatin

Systematic (IUPAC) name

[(1*S*,3*R*,7*R*,8*S*,8*aR*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxo-oxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8*a*-hexahydronaphthalen-1-yl]2,2-dimethylbutanoate

Identifiers	
CAS number	79902-63-9 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=79902-63-9&rn=1)
ATC code	C10AA01 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=C10AA01)
PubChem	54454 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=54454)
DrugBank	APRD00104 (http://www.drugbank.ca/cgi-bin/show_drug.cgi?CARD=APRD00104)
Chemical data	
Formula	$C_{25}H_{38}O_5$
Mol. mass	418.566 g/mol
SMILES	eMolecules (http://www.emolecules.com/cgi-bin/search?t=ex&q=CCC%28C%29%28C%29C%28%3DO%29O%5BC%40H%5D1C%5BC%40%40H%5D%28C%29C%3DC2C%3DC%5BC%40H%5D%28C%29%5BC%40H%5D%28CC%5BC%40%40H%5D3C%5BC%40%40H%5D%28O%29CC%28%3D+O%29O3%29%5BC%40%40H%5D12) & PubChem (http://pubchem.ncbi.nlm.nih.gov/search/?smarts=CCC%28C%29%28C%29C%28%3DO%29O%5BC%40H%5D1C%5BC%40%40H%5D%28C%29C%3DC2C%3DC%5BC%40H%5D%28C%29%5BC%40H%5D%28CC%5BC%40%40H%5D3C%5BC%40%40H%5D%28O%29CC%28%3D+O%29O3%29%5BC%40%40H%5D12)
Metabolism	Hepatic (CYP3A4)
Half life	2 hours
Excretion	Renal 13%, faecal 60%
Therapeutic considerations	
Pregnancy cat.	X
Pharmacokinetic data	
Bioavailability	5%

Protein binding	95%
Legal status	D(AU) X(US) Prescription Only (S4)(AU) P(UK) R-only(US)
Routes	Oral

extract by Karl Folkers, Carl Hoffman, and others at Merck; while Huff and his associates confirmed that mevalonic acid was an intermediate in cholesterol biosynthesis. In 1959, the HMG-CoA reductase enzyme (a major contributor of internal cholesterol production) was discovered by researchers at the Max Planck Institute. This discovery encouraged scientists worldwide to find an effective inhibitor of this enzyme.

By 1976, Akira Endo had isolated the first inhibitor (Compactin, ML-236B) from the fungus, *Penicillium citrinium* in Sankyo, Japan.[1] In 1979, Hoffman and colleagues isolated lovastatin from a strain of the fungus *Aspergillus terreus*. While developing and researching lovastatin, Merck scientists synthetically derived a more potent HMG-CoA reductase inhibitor from a fermentation product of *Aspergillus terreus*, which was designated MK-733 (later to be named simvastatin).[2]

Uses

Simvastatin is a powerful lipid-lowering drug that can decrease low density lipoprotein (LDL) levels by up to 50%. It is used in doses of 5 mg up to 80 mg. Higher doses (160 mg) have been found to be too toxic, while giving only minimal benefit in terms of lipid lowering. There is no real effect on HDL and triglyceride levels.

From recent research it has become apparent that simvastatin and other statins inhibit the progression of atherosclerosis beyond their effects on LDL. Many explanations have been proposed, for example its inhibitory effect on macrophages in the atherosclerotic plaque lesions.

In one non-randomized study, simvastatin halved the risk of developing dementia or Parkinson's disease. [3]

Rationing

Since its introduction, there has been a large debate surrounding the price for lipid-lowering treatment and its benefits on atherosclerosis. Although this has affected the other statins as well, simvastatin was the first statin drug to be used extensively in clinical practice.

A number of large epidemiological studies were conducted to discover which patients would benefit most from statin drugs; most studies involve simvastatin as the study drug. The most influential studies were the Scandinavian Simvastatin Survival Study (4S) and the Heart protection study (HPS).

It has now become apparent that patients with one or more risk factors for cardiovascular disease (such as diabetes mellitus, hypertension or a positive family history) can benefit from statins—even if they do not have substantially elevated cholesterol levels.

Simvastatin was introduced in the late 1980s, and in many countries it is now available as a generic preparation. This has led to a decrease of the price of most statin drugs, and a reappraisal of the health economics of preventive statin treatment.

In the UK, simvastatin (in a dose of 10 mg) has recently become available to purchase from pharmacies without prescription.

Pharmacology

All statins act by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the HMG-CoA reductase pathway, the metabolic pathway responsible for the endogenous production of cholesterol.

The drug is in the form of an inactive lactone that is hydrolized after ingestion to produce the active agent. It is a white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Interactions

Grapefruit contains the flavonoid naringenin and furanocoumarin bergamottin, which inhibit the liver cytochrome P450 3A4. This in turn slows metabolization of simvastatin and a large number of other drugs. Therefore, patients taking simvastatin should restrict their intake of grapefruit and grapefruit-containing products.

Side effects

Common side effects (>1% incidence) may include abdominal pain, diarrhea, indigestion, and a general feeling of weakness. Rare side effects include joint pain, memory loss, and muscle cramps.[4][5]

Marketing

Reference: Drug Discovery Today editorial, 2005.[6]

Zocor Logo

Simvastatin was initially marketed by Merck & Co under the trade name **Zocor**, but is now also available generically in most countries following the patent expiry. A combination of Simvastatin along with Ezetimibe is currently sold under the brand name Vytorin and is jointly marketed by Merck and Schering-Plough.

Brand names: Zocor, Zocor Heart Pro, marketed by the pharmaceutical company Merck & Co. Simlup,Simvotin, Simcard [India] Denan (Germany), Liponorm, Sinvacor, Sivastin (Italy), Lipovas (Japan), Lodales (France), Zocord (Austria and Sweden), Zimstat, Simvahexal (Australia), Lipex (Australia and New Zealand), Simvastatin-Teva, Simvacor, Simvaxon, Simovil (Israel)and others.

The primary US patent for Zocor expired on June 23, 2006; Ranbaxy Laboratories (at the 80-mg strength) and Teva Pharmaceutical Industries through its Ivax Pharmaceuticals unit (at all other strengths) were given approval by the FDA to manufacture and sell simvastatin as a generic drug with

180-day exclusivity. Dr. Reddy's Laboratories also has a license from Merck & Co. to sell simvastatin as an authorized generic drug.

Ezetimibe/simvastatin is a combination product to lower lipids and marketed as Vytorin.

Sales

Prior to losing U.S. patent protection, simvastatin was Merck & Co.'s largest selling drug and second largest selling cholesterol lowering drug in the world; it recorded 4.3 billion dollars of sales in 2005.[6] Zocor had an original patent expiration date of January 2006 but was extended by the United States Food and Drug Administration (FDA) to expire on June 23, 2006. The FDA granted the patent extension after Merck & Co, Inc. submitted data from studies of the drug's positive effect on children, a move typically used by drug companies to lengthen exclusivity.[6]

Ordinarily, Merck & Co. would have expected a sharp decrease in sales after the generic versions of simvastatin entered the market; however, Merck has slashed the price of Zocor dramatically in an effort to claim sales that would have otherwise gone to the generic versions. At least two major U.S. health insurers, UnitedHealthcare and WellPoint, are now offering Zocor to their members at generic copays.[7]

In addition, since Merck & Co. itself manufactures at least some versions of Dr. Reddy's authorized generic simvastatin. Merck & Co. is also poised to profit from the Dr. Reddy's version. An 80 mg, 30-count bottle of Dr. Reddy's simvastatin obtained July 6, 2006, states it is made by Merck Sharp & Dohme (Merck & Co.'s name outside the US to avoid conflicts with Merck KGaA) in the UK, just like 80 mg Zocor, and has a Merck & Co. logo on the bottom; except for omitting the "80" on one side, the tablets are visually identical to 80 mg Zocor, including "543" on the other side which is the key part of the National Drug Code for 80 mg Zocor.

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See also

- List of drugs affected by grapefruit

External links

- RxList.com (http://www.rxlist.com/cgi/generic/simva.htm) - Simvastatin

Retrieved from "http://en.wikipedia.org/wiki/Simvastatin"
Categories: Merck | Statins

Ezetimibe

From Wikipedia, the free encyclopedia

Ezetimibe (pronounced /ɛ'zɛtəmɪb/) is an anti-hyperlipidemic medication which is used to lower cholesterol levels. It acts by decreasing cholesterol absorption in the intestine. It may be used alone when other cholesterol-lowering medications are not tolerated, or together with statins (e.g. ezetimibe/simvastatin, marketed as **Vytorin** and **Inegy**) when cholesterol levels are unable to be controlled on statins alone. It is marketed by Schering-Plough and Merck under the trade names **Ezetrol, Zetia** and **Ezemibe**. Ezetimibe was originally discovered by a team of four Schering-Plough research chemists: Drs. Stuart B. Rosenblum, Duane A. Burnett, John W. Clader and Brian A. McKittrick.

Contents

- 1 Pharmacology
- 2 Clinical use
  - 2.1 Indications
  - 2.2 Adverse effects
  - 2.3 Dosage forms
- 3 Clinical trial controversy
- 4 References
- 5 See also
- 6 External links

Ezetimibe

Systematic (IUPAC) name

(3*R*,4*S*)-1-(4-fluorophenyl)-3-((3*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)-2-azetidinone

Identifiers

CAS number	163222-33-1 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=163222-33-1&rn=1)
ATC code	C10AX09 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=C10AX09)
PubChem	150311 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=150311)
DrugBank	APRD00619 (http://www.drugbank.ca/cgi-bin/show_drug.cgi?CARD=APRD00619)

Chemical data

Formula	$C_{24}H_{21}F_2NO_3$
Mol. mass	409.4 g.mol^{-1}
SMILES	eMolecules (http://www.emolecules.com/cgi-bin/search?t=ex&q=Oc1ccc%28cc1%29%5BC%40%40H%5D1%5BC%40%40H%5D%28CC%5BC%40H%5D%28O%29c2ccc%28F%29cc2%29C%28%3DO%29N1c1ccc%28F%29cc1) & PubChem (http://pubchem.ncbi.nlm.nih.gov/search/?smarts=Oc1ccc%28cc1%29%5BC%40%40H%5D1%5BC%40%40H%5D%28CC%5BC%40H%5D%28O%29c2ccc%28F%29cc2%29C%28%3DO%29N1c1ccc%28F%29cc1)

Pharmacokinetic data

Bioavailability	35–65%
Protein binding	>90%
Metabolism	Intestinal and hepatic
Half-life	~22 hours

Therapeutic considerations

Pregnancy cat.	C (Au), C (U.S.)
Legal status	℞-only (U.S.)
Routes	Oral

Pharmacology

Excretion	Renal 11%, faecal 78%

Ezetimibe localises at the brush border of the small intestine, where it inhibits the absorption of cholesterol from the diet. Specifically, it appears to bind to a critical mediator of cholesterol absorption, the Niemann-Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells[1] as well as in hepatocytes[2]. In addition to this direct effect, decreased cholesterol absorption leads to an increase in LDL-cholesterol uptake into cells, thus decreasing levels in the blood plasma.

Clinical use

Indications

Ezetimibe is indicated as an adjunct to dietary measures in the management of:

- Hypercholesterolaemia
- Homozygous sitosterolemia (phytosterolemia)[3]

On 9 June 2006, U.S. regulators approved the use of ezetimibe in combination with fenofibrate to treat mixed hyperlipidaemia.

Adverse effects

Common adverse drug reactions ($\geqslant$1% of patients) associated with ezetimibe therapy include: headache and/or diarrhea. Infrequent adverse effects (0.1–1% of patients) include: myalgia and/or raised liver function test (ALT/AST) results. Rarely (<0.1% of patients), hypersensitivity reactions (rash, angioedema) or myopathy may occur.[3]

Dosage forms

Ezetimibe is available as 10 mg tablets in most markets. A combination preparation ezetimibe/simvastatin, which combines ezetimibe with a statin, is also available.

Zetia® (ezetimibe)

Zetia Logo

Clinical trial controversy

On January 14, 2008, it was reported in the *New York Times* that a clinical trial (ENHANCE trial) of Zetia that was designed to show that the drug could reduce the growth of fatty plaques in arteries instead resulted in *growth* of plaques. However, the growth noted was less than it would have been had the patients been on placebo alone. Merck and Schering-Plough completed the clinical trial in April 2006 and had initially planned to release the findings no later than March 2007. The companies missed several self-imposed deadlines, and in December 2007, finally agreed to publish the results "soon" after the delays were publicized in news reports.[4]

It should be recognized that the ENHANCE trial was not a clinical-outcome trial, but merely an imaging study. Formally, the American College of Cardiology (ACC) maintains that Zetia may be a reasonable option for patients who cannot tolerate a statin or cannot be controlled on a high dose statin. [5] Results from the trial have provoked three large clinical-outcome trials. The results from these trials will be presented in the next three to four years. However, a March 30th, 2008 meeting of the ACC resulted in negative press for drugs like Zetia as Yale University Cardiologist Harlan Krumholz and concurring colleagues called into question the efficacy of such drugs. [6] Krumholz' statements maintained that such pharmaceuticals should not be the first or even second option for prescribing doctors. Definitive conclusions of the efficacy and safety of Zetia can be made such a time when the results of more substantial and comprehensive trials are released, such as the upcoming IMPROVE-IT Trial which has an enrollment of 18000 patients and will report results in 2012.

References

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5. ^ "ACC Statement on ENHANCE Trial (http://acc.org/enhance.htm)", ACC (2008-01-15). Retrieved on 2008-02-04.
6. ^ Carey, J (2008-03-31). "A Weak Prognosis for Vytorin and Zetia (http://www.businessweek.com/bwdaily/dnflash/content/mar2008/db20080331_704360.htm?)", Business Week. Retrieved on 2008-04-01.

See also

- Ezetimibe/simvastatin
- Statin

External links

- Zetia (http://www.zetia.com/)
- U.S. Prescribing Information (http://www.zetia.com/ezetimibe/zetia/consumer/product_information/pi/index.jsp)

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(3) tax-deductible nonprofit charity.